

## **Developing stem cell therapies for Friedreich's Ataxia**

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### **Scientific Summary**

Friedreich's ataxia (FA) is the commonest autosomal recessive ataxic condition. The disease is characterised by neurodegeneration of large sensory neurones, dorsal root ganglia and spinocerebellar tracts. Mechanisms of neurodegeneration include defects in mitochondrial respiratory chain function and increased oxidative damage, but currently no treatment has been shown to reduce disease progression. We are interested in whether bone marrow transplantation may be a useful therapy for FA and we have shown that human bone marrow-derived stem cells are able to protect cerebellar neurones *in vitro*. We have also defined specific intracellular mechanisms underlying these effects and shown that human stem cells can be induced to adopt a neuronal phenotype under a variety of conditions, possibly either by transdifferentiation or cell fusion. The proposed project aims to further explore this possibility by defining the precise neuroprotective role of bone marrow-derived stem cells; transplanting stem cells into an animal model of FA; and studying the process of cell fusion, which may be a novel neuroprotective mechanism. Autologous bone marrow transplantation has many advantages as a treatment, not least its safety profile, and is being trialed as a potential treatment for other neurological disorders. We believe it may be a potential therapy for FA in due course.

### **Lay Summary:**

Friedreich's ataxia (FA) is characterised by degeneration of a variety of cells within the body including nerve cells. Abnormalities in the balance part of the brain, called the cerebellum, give rise to the symptom of ataxia. Current evidence suggests that the genetic defect causing FA leads to reduction in amounts of energy available to nerve cells and also accumulation of toxic substances which may be poorly handled by diseased cells. Future treatments for FA will need to address these issues and provide protection for nerve cells. We are particularly interested in the potential for bone marrow-derived stem cells as treatments for a number of neurological conditions. These cells have the advantage that they may be derived from the patient's own bone marrow, thus avoiding rejection and a large number of ethical issues concerning stem cells. Furthermore bone marrow transplants have been used for many years for the treatment of several haematological conditions and thus much safety data is available. We have carried out initial research demonstrating that in cell culture human bone marrow-derived stem cells are able to improve the survival of cells derived from the cerebellum. We have also shown that these stem cells can

integrate within the nervous system following transplantation in animal models, thus establishing that bone marrow derived cells may be able to protect or even replace lost brain cells. These studies are now at a critical stage and we wish to investigate this further in an animal model of FA. Specifically, we aim to determine whether transplantation of human bone marrow-derived stem cells will protect against progression of disease in an animal model of FA. These are vital pre-requisites before commencing human trials. We hope these studies will, in time, lead to the establishment of clinical trials of stem cell therapies for FA.

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